BRAVELLE - urofollitropin
FERRING PHARMACEUTICALS INC.

DESCRIPTION

Bravelle® is a product containing a highly purified preparation of human follicle stimulating hormone (hFSH) extracted from the urine of postmenopausal women. Human FSH consists of two non-covalently linked glycoproteins designated as the α and β subunits. The α subunit has 92 amino acids of which two are modified by attachment of carbohydrates. The β subunit has 111 amino acids of which two are modified by attachment of carbohydrates.

Bravelle® is a sterile, lyophilize powder intended for subcutaneous (SC) or intramuscular (IM) injection after reconstitution with sterile 0.9% Sodium Chloride Injection, USP Each vial of Bravelle® contains 82.5 International Units (IU) of Follicle Stimulating Hormone (FSH) activity, 23 mg Lactose Monohydrate, 0.005 mg Polysorbate 20, and Sodium Phosphate buffer (Sodium Phosphate dibasic, Heptahydrate and Phosphoric acid) for pH adjustments, which, when reconstituted with diluent, will deliver 75 IU of FSH. Bravelle® contains up to 2% luteinizing hormone (LH) activity based on bioassay. Human Chorionic Gonadotropin (hCG) is not detected in Bravelle®. When stored at 3° to 25°C, up to 40% of the α subunits may be oxidized.
The in vivo biological activity of urofollitropin for injection, purified is determined by using reference standards calibrated against the First International Standard for follicle-stimulating hormone, (FSH, Urofollitropin), Urinary, Human for Bioassay, National Institute for Biological Standards and Control (NIBSC) at its 46th meeting in 1995.
FSH is a glycoprotein that is acidic and water-soluble.
Therapeutic class: Infertility.

CLINICAL PHARMACOLOGY

Bravelle® administered for 7 to 12 days produces ovarian follicular growth in women who do not have primary ovarian failure. Treatment with Bravelle® in most instances results only in follicular growth and maturation. When sufficient follicular maturation has occurred, hCG must be given to induce ovulation.

PHARMACOKINETICS

Single doses of 225 IU and multiple daily doses (7 days) of 150 IU of Bravelle® were administered to healthy volunteer female subjects while their endogenous FSH was suppressed. Sixteen subjects received Bravelle® SC and 12 received the drug IM. Serum FSH concentrations were determined. Based on the steady state ratio of FSH Cmax and AUC, SC and IM administration of Bravelle® were not bioequivalent. Multiple doses of Bravelle® IM resulted in C_{max} and AUC of 77.7% and 81.8% compared to multiple doses of Bravelle® SC. The FSH pharmacokinetic parameters for single and multiple dose Bravelle®, administered SC and IM are in Table 1.

Table 1. FSH Pharmacokinetic Parameters Following Bravelle® Administration

	Single Dose (225 IU)		Multiple Dose X 7 (150 IU)	
PK Parameters	SC	IM	SC	IM
Cmax (mIU/mL)	6.0 (1.7)	8.8 (4.5)	14.8 (2.9)	11.5 (2.9)
T_{max} (hrs)	20. (7.7)	17.4 (12.2)	9.6 (2.1)	11.3 (8.4)
AUCobs (mlU•hr/mL)	379 (111)	331 (179)	234.7 (77.0)	192.1 (52.3)
$T_{1/2}$ (hrs)	31.8	37	20.6	15.2
Ka (hr^{-1})	0.0500 (0.0231)	0.1408 (0.1227)	0.0905 (0.0383)	0.0358 (0.0108)

Absorption

The maximum plasma concentration of FSH was attained at 20.5 and 17.4 hours following SC and IM single dose administration, respectively. However, following multiple dosing, it was attained at approximately 10 hours following both routes of administration.

Distribution

Human tissue or organ distribution of FSH has not been studied for Bravelle®.

Metabolism

Metabolism of FSH has not been studied for Bravelle® in humans.

Elimination
The mean elimination half-lives of FSH for SC and IM single dosing are 31.8 and 37 hours, respectively. However, following multiple dosing (X 7 days) they are 20.6 and 15.2 hours for SC and IM, respectively.

Pediatric Populations
Bravelle® is not indicated in pediatric populations.

Geriatric Populations
Bravelle® is not indicated in geriatric populations.

Special Populations
The safety and efficacy of Bravelle® in renal and hepatic insufficiency have not been studied.

Drug Interactions
No drug/drug interaction studies have been conducted for Bravelle® in humans.

CLINICAL STUDIES
The efficacy of Bravelle® was established in two randomized, active controlled, multi-center studies, one for in-vitro fertilization [IVF] and one for ovulation induction [0I].

Ovulation Induction
In the randomized, controlled ovulation induction study, patients underwent pituitary suppression with a GnRH agonist before being randomized to Bravelle® SC, Bravelle®- IM or a commercial recombinant FSH product administered SC. A total of 111 oligo-anovulatory patients were randomized of whom 72 received Bravelle®, starting at a dose of 150 IU daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily Based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed 12 days. Results for the Intent-To-Treat Population are summarized in Table 2.

Table 2. Efficacy Outcome by Treatment Groups in Ovulation Induction for Study FPI FSH 99-03 (one cycle of treatment)

	Bravelle®SC	Bravelle® IM
Parameter	N=35	N=37
Ovulation (%)	24 (68.6)	26 (70.3)
Received hCG (%)	25(71.4)	28 (75.7)
Mean Peak Serum E_2 (pg/mL) (SD)	976.5 (680.6)	893.2 (815.2)
Chemical Pregnancy (%)	11 (31.4)	8 (21.6)
Clinical Pregnancy (%)	9(25.7)	7(18.9)
Continuing Pregnancy (%)	9(25.7)	7(18.9)
Pts. w/Live Births (%)	9(25.7)	6(16.2)

Assisted Reproductive Technologies [ART]
In the randomized, controlled IVF study FPI FSH 2001-01, patients underwent pituitary suppression with a GnRH agonist before being randomized to Bravelle® SC or a commercial recombinant FSH product administered SC. A total of 120 patients were randomized of whom 60 received Bravelle®, starting at a dose of 225 IU daily for 5 days. This was followed by individual titration of the dose from 75 to 450 IU daily based on ultrasound and estradiol (E_2) levels. The total duration of dosing did not exceed 12 days. Results are summarized in Table 3 for the Intent-To-Treat population.

Table 3. Efficacy Outcome for IVF Study FPI FSH 2001-01 (one cycle of treatment)

	Bravelle®SC
Parameter	n=60
Mean Total Oocytes Retrieved Per Patient (SD)	11.8 (6.3)
Mean Mature Oocytes Retrieved	9.0 (5.7)

Per Patient (SD)	
Patients with Oocyte Retrieval (%)	57 (95.0)
Patients with Embryo Transfer (%)	57 (95.0)
Patients with Chemical Pregnancy (%)	28 (46.6)
Patients with Clinical Pregnancy (%)	25 (41.7)
Patients with Continuing Pregnancy (%)	23 (38.3)

INDICATIONS AND USAGE

Ovulation Induction

Bravelle® administered SC or IM in conjunction with hCG, is indicated for ovulation induction in patients who have previously received pituitary suppression.

Multifollicular Development during ART

Bravelle® administered SC in conjunction with hCG is indicated for multiple follicular development (controlled ovarian stimulation) during ART cycles in patients who have previously received pituitary suppression.

Selection of Patients

1. Before treatment with Bravelle® is instituted, a thorough gynecologic and endocrinologic evaluation must be performed. Except for those patients enrolled in an *in vitro* fertilization program, this should include a hysterosalpingography (to rule out uterine and tubal pathology) and documentation of anovulation by means of basal body temperature, serial vaginal smears, examination of cervical mucus, determination of serum (or urine) progesterone, urinary pregnanediol and endometrial biopsy. Patients with tubal pathology should receive Bravelle® only if enrolled in an *in vitro* fertilization program.
2. Primary ovarian failure should be excluded by the determination of gonadotropin levels.
3. Careful examination should be made to rule out the presence of an early pregnancy.
4. Patients in late reproductive life have a greater predilection to endometrial carcinoma as well as a higher incidence of anovulatory disorders. Cervical dilation and curettage should always be done for diagnosis before starting Bravelle® therapy in such patients who demonstrate abnormal uterine bleeding or other signs of endometrial abnormalities.
5. Evaluation of the husband's fertility potential should be included in the workup.

CONTRAINDICATIONS

Bravelle® is contraindicated in women who have:

1. A high FSH level indicating primary ovarian failure.
2. Uncontrolled thyroid and adrenal dysfunction.
3. An organic intracranial lesion such as pituitary tumor.
4. The presence of any cause of infertility other than anovulation.
5. Abnormal bleeding of undetermined origin.
6. Ovarian cysts or enlargement not due to polycystic ovary syndrome.
7. Prior hypersensitivity to urofollitropins, purified.
8. Bravelle® is contraindicated in women who are pregnant and may cause fetal harm when administered to a pregnant woman. There are limited human data on the effects of Bravelle® when administered during pregnancy.

WARNINGS

Bravelle® is a drug that should only be used by physicians who are thoroughly familiar with infertility problems. It is a potent gonadotropic substance capable of causing Ovarian Hyperstimulation Syndrome [OHSS] with or without pulmonary or vascular complications in women. Bravelle® therapy requires a certain time commitment by physicians and supportive health professionals,

and its use requires the availability of appropriate monitoring facilities (see PRECAUTIONS - Laboratory Tests). Bravelle® should be used with a great deal of care.

Overstimulation of the Ovary During Bravelle® Therapy

Ovarian Enlargement: Mild to moderate uncomplicated ovarian enlargement which may be accompanied by abdominal distension and/or abdominal pain occurs in approximately 20% of those treated with follitropin and hCG, and generally regresses without treatment within two or three weeks.

In order to minimize the hazard associated with the occasional abnormal ovarian enlargement, which may occur with FSH - hCG therapy, the lowest dose consistent with expectation of good results should be used. Careful monitoring of ovarian response can further minimize the risk of overstimulation.

If the ovaries are abnormally enlarged on the last day of Bravelle® therapy, hCG should not be administered in the course of therapy; this will reduce the chances of development of the Ovarian Hyperstimulation Syndrome.

OHSS: OHSS is a medical event distinct from uncomplicated ovarian enlargement. OHSS may progress rapidly to become a serious medical event. It is characterized by an apparent dramatic increase in vascular permeability, which can result in a rapid accumulation of fluid in the peritoneal cavity, thorax, and potentially, the pericardium. The early warning signs of development of OHSS are severe pelvic pain, nausea, vomiting, and weight gain. The following symptomatology has been seen with cases of OHSS: abdominal pain, abdominal distension, gastrointestinal symptoms including nausea, vomiting and diarrhea, severe ovarian enlargement, weight gain, dyspnea, and oliguria. Clinical evaluation may reveal hypovolemia, hemoconcentration, electrolyte imbalances, ascites, hemoperitoneum, pleural effusions, hydrothorax, acute pulmonary distress, and thromboembolic events (see "Pulmonary and Vascular Complications" below). Transient liver function test abnormalities suggestive of hepatic dysfunction, which may be accompanied by morphologic changes on liver biopsy, have been reported in association with the Ovarian Hyperstimulation Syndrome (OHSS).

In a clinical study of ovulation induction, 6 of 72 (8.33%) Bravelle® treated women developed OHSS and two were classified as severe. In a clinical study for multiple follicular development during IVF, 3 of 60 Bravelle® treated women developed OHSS and 1 was classified as severe. Cases of OHSS are more common, more severe and more protracted if pregnancy occurs. OHSS develops rapidly; therefore patients should be followed for at least two weeks after hCG administration. Most often, OHSS occurs after treatment has been discontinued and reaches its maximum at about 7 to 10 days after treatment. Usually, in cases where OHSS may be developing prior to hCG administration (see PRECAUTIONS - Laboratory Tests), the hCG should be withheld.

If severe OHSS occurs, treatment *must* be stopped and the patient should be hospitalized.

A physician experienced in the management of the syndrome, or who is experienced in the management of fluid and electrolyte imbalances should be consulted.

Pulmonary and Vascular Complications

Serious pulmonary conditions (e.g. atelectasis, acute respiratory distress syndrome) have been reported. In addition, thromboembolic events both in association with, and separate from, the Ovarian Hyperstimulation Syndrome have been reported following FSH therapy. Intravascular thrombosis and embolism, which may originate in venous or arterial vessels, can result in reduced blood flow to critical organs or the extremities. Sequelae of such events have included venous thrombophlebitis, pulmonary embolism, pulmonary infarction, cerebral vascular occlusion (stroke), and arterial occlusion resulting in loss of limb. In rare cases, pulmonary complications and/or thromboembolic events have resulted in death.

Multiple Pregnancies

Multiple pregnancies have occurred following treatment with Bravelle® SC and IM.

Pregnancy outcomes in a controlled study of 72 patients undergoing ovulation induction with Bravelle® are shown in Table 4.

Table 4. FPI FSH 99-03 Outcome of Pregnancies

	Bravelle® SC	Bravelle® IM
Parameter	N(%)	N(%)
Total Continuing Pregnancies	9(100)	7(100)
Singlets	3(33.3)	5(71.4)
Total No. with Multiple Pregnancies	6(66.7)	2(28.6)
Twins	4	0
Triplets	2	0
Quadruplets	0	1
Quintuplets	0	0
Sextuplets	0	1

The pregnancy outcomes in a controlled study of 60 patients undergoing treatment with Bravelle® in IVF are shown in Table 5.
Table 5. FPI FSH 2001-01 Outcome of Pregnancies

	Bravelle®SC
Parameter (%)	N(%)
Total No. of Continuing Pregnancies	23(100)
Singlets	15 (65.2)
Total No. of Multiple Pregnancies	8 (34.8)
Twins	5
Triplets	3

The patient and her partner should be advised of the potential risk of multiple births before starting treatment.
Hypersensitivity/Anaphylactic Reactions Hypersensitivity/anaphylactic reactions associated with follitropins for injection, purified administration have been reported in some patients. These reactions presented as generalized urticaria, facial edema, angioneurotic edema, and/or dyspnea suggestive of laryngeal edema. The relationship of these symptoms to uncharacterized urinary proteins is uncertain.

PRECAUTIONS

General

Careful attention should be given to the diagnosis of infertility in the selection of candidates for Bravelle® therapy (see **"INDICATIONS AND USAGE**-Selection of patients")

Information for Patients

Prior to therapy with Bravelle® patients should be informed of the duration of treatment and the monitoring of their condition that will be required. Possible adverse reactions (see ADVERSE REACTIONS section) and the risk of multiple births should also be discussed.

Laboratory Tests

The combination of both estradiol levels and ultrasonography are useful for monitoring the growth and development of follicles, timing hCG administration, as well as minimizing the risk of the Ovarian Hyperstimulation Syndrome and multiple gestations.
The clinical confirmation of ovulation, is determined by:
a. A rise in basal body temperature,
b. Increase in serum progesterone, and
c. Menstruation following the shift in basal body temperature.
When used in conjunction with indices of progesterone production, sonographic visualization of the ovaries will assist in determining if ovulation has occurred. Sonographic evidence of ovulation may include the following:
a. Fluid in the cul-de-sac,
b. Ovarian stigmata, and
c. Collapsed follicle.
Because of the subjectivity of the various tests for the determination of follicular maturation and ovulation, it cannot be overemphasized that the physician should choose tests with which he/she is thoroughly familiar.

Carcinogenesis and Mutagenesis

Long-term toxicity studies in animals and in vitro mutagenicity tests have not been performed to evaluate the carcinogenic potential of urofollitropin for injection, purified.

Pregnancy

Pregnancy Category X: See **CONTRAINDICATIONS** section.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in the nursing infant from Bravelle®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients

Safety and effectiveness in pediatric patients have not been established.

Geriatric Patients

Safety and effectiveness in geriatric patients have not been established.

ADVERSE REACTIONS

The safety of Bravelle® was examined in four clinical studies that enrolled a total of 222 patients receiving Bravelle® including 72 for ovulation induction and 150 for IVF.

All adverse events (without regard to causality assessment) occurring ≥ 2 % incidence in the clinical study patients receiving Bravelle® are listed in Table 6, (FPI FSH 99-03 study for ovulation induction) and Table 7 (FPI FSH 99-04, FPI FSH 99-05 and FPI FSH 2001-01 studies for IVF).

Table 6. FPI FSH 99-03 Ovulation Induction Safety Profile

All Patients with Adverse Events ≥ 2%		
Adverse Events(%)	Bravelle® SC	Bravelle® IM
	N=35	N=37
Genitourinary/Reproductive		
OHSS	4(11.4)	2(5.4)
Vaginal Hemorrhage	3(8.6)	0(0.0)
Ovarian Disorder (Pain, Cyst)	1 (2.9)	3(8.1)
Urinary tract infection	0	1 (2.7)
Cervix disorder	1 (2.9)	0
Gastrointestinal		
Nausea	2 (5.7)	0(0.0)
Enlarged Abdomen	1 (2.9)	1 (2.7)
Abdominal Pain	1 (2.9)	2 (5.4)
Vomiting	0	1 (2.7)
Constipation	0	1 (2.7)
Diarrhea	0	1 (2.7)
Metabolic/Nutritional		
Dehydration	0	1 (2.7)
Weight gain	1 (2.9)	0
Skin/Appendages		
Acne	1 (2.9)	0
Exfoliative dermatitis	0	1 (2.7)
Other Body Systems		
Headache	4(11.4)	3(8.1)
Pain	2(5.7)	0(0.0)
Neck pain	0	1 (2.7)
Respiratory Disorder	2 (5.7)	0 (0.0)
Hot Flashes	2(5.7)	0(0.0)
Fever	0	1 (2.7)
Hypertension	0	1 (2.7)
Emotional lability	0	1 (2.7)
Depression	0	1 (2.7)
Accidental injury	0	1 (2.7)

Table 7. Integrated IVF Safety Profile

All Patients with Adverse Events ≥ 2%	
Adverse Events (%)	Bravelle® SC N=150
Genitourinary/Reproductive	
Vaginal hemorrhage	7(4.7)
Post retrieval pain	12(8.0)
Pelvic pain/cramps	10.(6.7)

OHSS	9(6.0)
Uterine spasms	4(2.7)
Vaginal spotting	4(2.7)
Urinary tract infection	5 (3.3)
Ovarian disorder	3(2.0)
Breast tenderness	3 (2.0)
Vaginal Discharge	4(2.7)
Infection fungal	3 (2.0)
Gastrointestinal	
Abdominal cramps	21(14.0)
Nausea	13(8.7)
Abdominal pain	7(4.7)
Abdominal fullness/enlargement	10(6.7)
Constipation	3(2.0)
Other Body Systems	
Headache	19 (12.7)
Pain	8(5.3)
Rash	4(2.7)
Respiratory disorder	6 (4.0)
Sinusitis	3(2.0)
Injection site reaction	6(4.0)
Hot flash	6(4.0)
Emotional lability	3(2.0)

The following medical events have been reported subsequent to pregnancies resulting from gonadotropin therapy in published clinical studies:

1. Spontaneous Abortion
2. Ectopic Pregnancy
3. Premature Labor
4. Postpartum fever
5. Congenital abnormalities

The following adverse reactions have been previously reported during urofollitropin for injection, purified therapy:

1. Pulmonary and vascular complications (see **WARNINGS),**
2. Adnexal torsion (as a complication of ovarian enlargement),
3. Mild to moderate ovarian enlargement,
4. Hemoperitoneum,
5. There have been infrequent reports of ovarian neoplasms, both benign and malignant, in women who have undergone multiple drug regimens for ovulation induction; however, a causal relationship has not been established.

DRUG ABUSE AND DEPENDENCE

There have been no reports of abuse or dependence with follitropins.

OVERDOSAGE

Aside from possible ovarian hyperstimulation (see **WARNINGS**) and multiple gestations (see **WARNINGS),** little is known concerning the consequences of acute overdosage with Bravelle®

DOSAGE AND ADMINISTRATION

Dosage:

Infertile patients with oligo-anovulation: The dose of Bravelle® to stimulate development of ovarian follicles must be individualized for each patient. The lowest dose consistent with achieving good results based on clinical experience and reported clinical data should be used.

The recommended initial dose of Bravelle® for patients who have received GnRH agonist or antagonist pituitary suppression is 150 IU daily administered SC or IM for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle® should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

If patient response to Bravelle® is appropriate, hCG (5000 to 10,000 USP units) should be given 1 day following the last dose of Bravelle®. The hCG should be withheld if the serum estradiol is greater than 2000 pg/mL, if the ovaries are abnormally enlarged or if abdominal pain occurs, and the patient should be advised to refrain from intercourse. These precautions may reduce the risk of Ovarian Hyperstimulation Syndrome and multiple gestations. Patients should be followed closely for at least 2 weeks after hCG administration. If there is inadequate follicle development or ovulation without subsequent pregnancy, the course of treatment with Bravelle®may be repeated. The couple should be encouraged to have intercourse daily, beginning on the day prior to the administration of hCG until ovulation becomes apparent from the indices employed for the determination of progestational, activity. In the light of the foregoing indices and parameters mentioned, it should become obvious that, unless a physician is willing to devote considerable time to these patients and be familiar with and conduct the necessary laboratory studies, he/she should not use Bravelle®.

Assisted Reproductive Technologies: The recommended initial dose of Bravelle® for patients undergoing IVF and donor egg patients who have received GnRH agonist or antagonist pituitary suppression is 225 IU daily administered SC for the first 5 days of treatment. Based on clinical monitoring (including serum estradiol levels and vaginal ultrasound results) subsequent dosing should be adjusted according to individual patient response. Adjustments in dose should not be made more frequently than once every 2 days and should not exceed more than 75 to 150 IU per adjustment. The maximum daily dose of Bravelle® given should not exceed 450 IU and in most cases dosing beyond 12 days is not recommended.

Once adequate follicular development is evident, hCG (5,000-10,000 USP units) should be administered to induce final follicular maturation in preparation for oocyte retrieval. The administration of hCG must be withheld in cases where the ovaries are abnormally enlarged on the last day of therapy. This should reduce the chance of developing OHSS.

Directions for Using Bravelle®

1) Wash hands thoroughly with soap and water.
2) Before injections, the septum tops of the vials should be wiped with an aseptic solution to prevent contamination of the contents.
3) To prepare the Bravelle® solution, inject 1 mL of Sterile Saline for Injection, USP into the vial of Bravelle®. **DO NOT SHAKE,** but gently swirl until the solution is clear. Generally, the Bravelle® dissolves immediately. Check the liquid in the container. If it is not clear or has particles in it, **DO NOT USE IT.**
4) For patients requiring a single injection from multiple vials of Bravelle®, up to 6 vials can be reconstituted with 1 mL of Sterile Saline for Injection, USP. This can be accomplished by reconstituting a single vial as described above (see step 3). Then draw the entire contents of the first vial into a syringe, and inject the contents into a second vial of lyophilized Bravelle®. Gently swirl the second vial, as described above, once again checking to make sure the solution is clear and free of particles. This step can be repeated with 4 additional vials for a total of up to 6 vials of lyophilized Bravelle® into 1 mL of diluent.
5) Immediately **ADMINISTER** the reconstituted Bravelle® either **SC** (for ovulation induction or multifollicular development during ART) or **IM** (for ovulation induction). Any unused reconstituted material should be discarded.
6) Draw the reconstituted Bravelle® into an empty, sterile syringe.
7) Hold the syringe pointing upwards and gently tap the side to force any air bubbles to the top; then squeeze the plunger gently until all the air has been expelled and only Bravelle® solution is left in the syringe.

8) Bravelle® works if it is injected **SC** (for ovulation induction or multifollicular development during ART) or **IM** (for ovulation induction). The recommended sites for SC injection are either side of the lower abdomen in alternating fashion with the actual injection site varied a little with each injection. SC injection of Bravelle® into the thigh is not recommended unless the lower abdomen is not usable because of scarring, surgical deformity or other medical conditions.

The best site for IM injection of Bravelle® is the upper outer quadrant of the buttock muscle near the hip. This area contains few blood vessels and major nerves. Stretching the skin helps the needle to go in more easily and pushes the tissue beneath the skin out of the way. This helps the solution disperse correctly.

9) The injection site should be swabbed with a disinfectant to remove any surface bacteria. Clean about two inches around the point where the needle will go in and let the disinfectant dry for at least one minute before proceeding.
10) For **SC** injection, the needle should be inserted at a 90° angle to the skin surface.

For **IM** injection, the needle should be inserted at a 90° angle to the skin surface. Pushing in with a quick thrust causes the least discomfort.

11) If the needle is correctly positioned, it will be difficult to draw back on the plunger. Any blood drawn into the syringe means the needle tip has penetrated a vein or artery. If this happens, remove the syringe, cover the injection site with a swab containing disinfectant and apply pressure; the site should stop bleeding in a minute or two.
12) Once the needle is properly placed, depress the plunger **slowly** and steadily, so the solution is correctly injected and the skin or muscle tissue is not damaged.
13) Pull the syringe out quickly and apply pressure to the site with a swab containing disinfectant. A gentle massage of the site - while still maintaining pressure - helps disperse the Bravelle® solution and relieve any discomfort.
14) Use the disposable syringe only once and dispose of it properly.

HOW SUPPLIED

Bravelle® (urofollitropin for injection, purified) is supplied in a sterile, lyophilized, single dose vial containing 82.5 IU of FSH, to deliver 75 IU FSH after reconstituting with the diluent.
Each vial is available with an accompanying vial of sterile diluent containing 2 mL of 0.9% Sodium Chloride Injection, USP.
75 IU FSH activity, supplied as:
NDC 55566-8505-2: *Box* of 5 vials + 5 vials diluent.

NDC 55566-8505-6: *Box* of 5 vials + 5 vials diluent + 5 Q•Cap™ vial adaptors.
Lyophilized powder may be stored refrigerated or at room temperature (3° to 25° C/37° to 77°F). Protect from light. Use immediately after reconstitution. Discard unused material.
Rx only
Vials of sterile diluent of 0.9% Sodium Chloride Injection, USP, manufactured for Ferring Pharmaceuticals Inc.

Q•Cap™ manufactured by Bioject Inc., Tualatin, OR 97062
Manufactured for:
FERRING PHARMACEUTICALS INC.
SUFFERN, NY 10901
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Albuquerque, New Mexico 87107
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